

### Adherent uncontrolled adult persistent asthma: Characteristics and asthma outcomes

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#### Clinical Implications

- The higher disease burden in high-risk, high-adherent patients suggests that health care organizations and clinicians need to target this subgroup with higher level step-care, more asthma specialist care, attention to relevant comorbidities, and judicious use of existing and novel new biologicals.

#### TO THE EDITOR:

Asthma control depends on many factors of which patients' demographic characteristics, asthma severity, medication selection/efficacy, comorbidities, and adherence play important roles.<sup>1</sup> To provide optimal systemwide asthma care management and manage costs, health care organizations are challenged to identify high-risk uncontrolled patients.<sup>2</sup> Frequency of asthma exacerbations, excessive use of short-acting  $\beta_2$ -agonists (SABAs), and adherence to asthma medication dispensing represent 3 integral asthma parameters available from administrative data to help in the identification of such high-risk patients with asthma to deliver more intensive care.<sup>3</sup> Accordingly, we sought to identify, characterize, and determine asthma outcomes in a subgroup of high-risk patients with uncontrolled asthma who were adherent to controller medication and compare them with the rest of the cohort with persistent asthma.

We conducted a retrospective cohort study (see Figure E1, A, in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)) of adult patients with persistent asthma from a large managed care organization to compare characteristics and outcomes of a high-risk uncontrolled, high-adherent subgroup with those of other patients with persistent asthma. Electronic administrative pharmacy and health care data from Kaiser Permanente Southern California were used to identify 9546 patients aged 18 to 64 years who met the Health Effectiveness Data and Information Set (HEDIS) 2-year criteria for persistent asthma in 2009 and 2010,<sup>4</sup> did not manifest chronic obstructive lung disease and other major illnesses (Figure E1, B, in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)), and were continuously enrolled health plan members with pharmacy benefit from 2009 to 2011.

*Asthma exacerbations* were defined as asthma emergency department (ED) visits or hospitalizations or asthma outpatient visits encoded for acute exacerbations, status asthmaticus, acute asthma attack, uncontrolled asthma, or asthmatic bronchitis requiring systemic corticosteroid dispensing within  $\pm 7$  days of the visit.<sup>5</sup> At least 8 days separated a new exacerbation. *Excessive SABA dispensing* was defined as 7 or more canisters

dispensed per year.<sup>6</sup> Adherence was determined on the basis of a number of controller canister equivalents dispensed in a year (canisters of inhaled controller medications or 30-day supplies of oral controller medications).<sup>7</sup> Nine or more controller canister equivalents dispensed met HEDIS 75% level adherence criteria and was considered high-adherence.<sup>7</sup> Using baseline data during 2010, the following risk and adherence levels were defined: (1) high-risk: 2 or more asthma exacerbations or 7 or more SABA canisters dispensed, (2) low-risk: fewer than 2 asthma exacerbations and fewer than 7 SABA canisters dispensed, (3) high-adherence: 9 or more controller canister equivalents dispensed, and (4) low-adherence: fewer than 9 controller canister equivalents dispensed. From these definitions, adult patients with persistent asthma were categorized into 4 groups on the basis of asthma risk and adherence in 2010: high-risk, high-adherent (N = 1031), high-risk, low-adherent (N = 2472), low-risk, high-adherent (N = 2505), and low-risk, low-adherent (N = 3538) (Figure E1, B, in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)).

Negative binomial and Poisson regression models with robust error variance were used to estimate the adjusted rate ratio and risk ratio, respectively, and their 95% CIs, and to derive the *P* values. The analyses were adjusted for the following characteristics in 2010: age, sex, race/ethnicity, geocoded education, various types of health insurance, length of health plan enrollment, obesity, comorbidities (Charlson comorbidity index, gastroesophageal reflux, rhinitis, chronic sinusitis, pneumonia, eczema, nasal polyps), smoking status, allergist care, and Global Initiative for Asthma (GINA) step-care level.<sup>8</sup> SAS (version 9.3 for Windows, SAS Institute, Cary, NC) was used for all analyses, with statistical significance level set at *P* < .05 (2-tailed).

Baseline characteristics in 2010 revealed that high-risk patients exhibited more obesity, active smoking, Charlson comorbidity index, and other individual comorbidities, and by definition, more asthma exacerbations and excessive SABA use than did low-risk patients (Table I). In addition, high-risk, high-adherent patients appeared to have higher levels of GINA step-care than did all other subgroups, including the high-risk, low-adherent subgroup. The high-adherent patients more often received allergist care than did the low-adherent groups, but this care was of only low frequency (25.5% in the high-risk, high-adherent and 24.2% in the low-risk, high-adherent subgroups). The high-risk, low-adherent subgroup also had a high frequency of no inhaled corticosteroid or low-dose inhaled corticosteroid treatment (>40%), emphasizing the need for this group of patients to receive higher step-care treatment with more intensive controller therapy to improve asthma control.

During the outcome year in 2011, the overall rate of asthma exacerbations in the entire adult cohort with persistent asthma was 0.32 events per person-year (95% CI, 0.31-0.34). Compared with the low-risk subgroups, the high-risk subgroups exhibited statistically more asthma exacerbations, higher frequencies of asthma ED/hospitalizations, and 7 or more SABA canisters dispensed (*P* < .001) (Table II; see Table E1 in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)).

In multivariate analyses, compared with both the low-risk, high-adherent and the low-risk, low-adherent subgroups,

**TABLE I.** Comparison of demographic characteristics, comorbidities, and asthma burden in 2010 among adult patients with persistent asthma based on levels of risk and adherence in 2010\*

| Demographic characteristics/clinical features (2010)                      | High-risk, high-adherent (N = 1,031) | High-risk, low-adherent (N = 2,472) | Low-risk, high-adherent (N = 2,505) | Low-risk, low-adherent (N = 3,538) | Entire cohort (N = 9,546) |
|---------------------------------------------------------------------------|--------------------------------------|-------------------------------------|-------------------------------------|------------------------------------|---------------------------|
| Age (y), mean ± SD                                                        | 47.7 ± 12.0                          | 42.9 ± 13.3                         | 49.7 ± 11.3                         | 45.1 ± 12.7                        | 46.0 ± 12.7               |
| Sex: female                                                               | 602 (58.4)                           | 1,379 (55.8)                        | 1,677 (66.9)                        | 2,234 (63.1)                       | 5,892 (61.7)              |
| Ethnicity                                                                 |                                      |                                     |                                     |                                    |                           |
| White                                                                     | 499 (48.4)                           | 985 (39.8)                          | 1,400 (55.9)                        | 1,472 (41.6)                       | 4,356 (45.6)              |
| Black                                                                     | 151 (14.6)                           | 443 (17.9)                          | 225 (9.0)                           | 495 (14.0)                         | 1,314 (13.8)              |
| Hispanic                                                                  | 238 (23.1)                           | 688 (27.8)                          | 458 (18.3)                          | 1,005 (28.4)                       | 2,389 (25.0)              |
| Native American/Native Alaskan                                            | 1 (0.1)                              | 7 (0.3)                             | 8 (0.3)                             | 9 (0.3)                            | 25 (0.3)                  |
| Asian/Pacific Islander                                                    | 79 (7.7)                             | 158 (6.4)                           | 249 (9.9)                           | 266 (7.5)                          | 752 (7.9)                 |
| Multiple, others                                                          | 25 (2.4)                             | 58 (2.4)                            | 44 (1.8)                            | 93 (2.6)                           | 220 (2.3)                 |
| Unknown                                                                   | 38 (3.7)                             | 133 (5.4)                           | 121 (4.8)                           | 198 (5.6)                          | 490 (5.1)                 |
| Estimated median household income by geocoding (US \$), mean ± SD         | 69,198 ± 27,597                      | 65,682 ± 29,003                     | 73,125 ± 29,026                     | 68,111 ± 29,136                    | 68,915 ± 29,037           |
| Estimated education level < high school diploma by geocoding, mean % ± SD | 21.7 ± 16.3                          | 24.9 ± 18.3                         | 18.8 ± 15.0                         | 23.7 ± 18.2                        | 22.5 ± 17.4               |
| Body mass index (kg/m <sup>2</sup> )                                      |                                      |                                     |                                     |                                    |                           |
| Mean ± SD                                                                 | 32.1 ± 8.0                           | 31.8 ± 8.0                          | 30.5 ± 7.3                          | 31.2 ± 7.8                         | 31.3 ± 7.7                |
| Obese (≥30 kg/m <sup>2</sup> )                                            | 548 (53.2)                           | 1,285 (52.0)                        | 1,109 (44.3)                        | 1,699 (48.0)                       | 4,641 (48.6)              |
|                                                                           | (N = 1,000)                          | (N = 2,412)                         | (N = 2,458)                         | (N = 3,459)                        | (N = 9,329)               |
| Smoking status                                                            |                                      |                                     |                                     |                                    |                           |
| Yes                                                                       | 91 (8.8)                             | 273 (11.0)                          | 99 (4.0)                            | 216 (6.1)                          | 679 (7.1)                 |
| Passive                                                                   | 13 (1.3)                             | 48 (1.9)                            | 15 (0.6)                            | 37 (1.0)                           | 113 (1.2)                 |
| Quit                                                                      | 252 (24.4)                           | 580 (23.5)                          | 582 (23.2)                          | 779 (22.0)                         | 2,193 (23.0)              |
| Never                                                                     | 620 (60.1)                           | 1,405 (56.8)                        | 1,672 (66.7)                        | 2,266 (64.0)                       | 5,963 (62.5)              |
|                                                                           | (N = 976)                            | (N = 2,306)                         | (N = 2,368)                         | (N = 3,298)                        | (N = 8,948)               |
| Length of health plan enrollment (y), mean ± SD                           | 17.6 ± 10.6                          | 15.9 ± 9.8                          | 17.3 ± 11.1                         | 15.5 ± 10.1                        | 16.3 ± 10.4               |
| Insurance†                                                                |                                      |                                     |                                     |                                    |                           |
| Commercial                                                                | 919 (89.1)                           | 2,174 (87.9)                        | 2,295 (91.6)                        | 3,184 (90.0)                       | 8,572 (89.8)              |
| Medicaid or other state programs                                          | 65 (6.3)                             | 133 (5.4)                           | 71 (2.8)                            | 136 (3.8)                          | 405 (4.2)                 |
| Medicare                                                                  | 30 (2.9)                             | 46 (1.9)                            | 57 (2.3)                            | 79 (2.2)                           | 212 (2.2)                 |
| Private Pay                                                               | 46 (4.5)                             | 161 (6.5)                           | 132 (5.3)                           | 198 (5.6)                          | 537 (5.6)                 |
| Charlson comorbidity index, mean ± SD                                     | 1.2 ± 0.8                            | 1.1 ± 0.8                           | 1.0 ± 0.8                           | 1.0 ± 0.8                          | 1.1 ± 0.8                 |
| Rhinitis                                                                  | 369 (35.8)                           | 603 (24.4)                          | 907 (36.2)                          | 1,007 (28.5)                       | 2,886 (30.2)              |
| Gastroesophageal reflux                                                   | 192 (18.6)                           | 312 (12.6)                          | 459 (18.3)                          | 483 (13.7)                         | 1,446 (15.1)              |
| Chronic sinusitis                                                         | 181 (17.6)                           | 302 (12.2)                          | 388 (15.5)                          | 505 (14.3)                         | 1,376 (14.4)              |
| Pneumonia                                                                 | 56 (5.4)                             | 105 (4.2)                           | 54 (2.2)                            | 94 (2.7)                           | 309 (3.2)                 |
| Eczema                                                                    | 27 (2.6)                             | 51 (2.1)                            | 53 (2.1)                            | 58 (1.6)                           | 189 (2.0)                 |
| Nasal polyps                                                              | 25 (2.4)                             | 31 (1.3)                            | 50 (2.0)                            | 55 (1.6)                           | 161 (1.7)                 |
| Allergist visit                                                           | 263 (25.5)                           | 319 (12.9)                          | 606 (24.2)                          | 549 (15.5)                         | 1,737 (18.2)              |
| 12-mo GINA step-care level                                                |                                      |                                     |                                     |                                    |                           |
| Step 1                                                                    | 0 (0)                                | 531 (21.5)                          | 0 (0)                               | 451 (12.7)                         | 982 (10.3)                |
| Step 2                                                                    | 112 (10.9)                           | 371 (15.0)                          | 346 (13.8)                          | 540 (15.3)                         | 1,369 (14.3)              |
| Step 3                                                                    | 327 (31.7)                           | 857 (34.7)                          | 783 (31.3)                          | 1,368 (38.7)                       | 3,335 (34.9)              |
| Step 4                                                                    | 566 (54.9)                           | 696 (28.2)                          | 1,358 (54.2)                        | 1,166 (33.0)                       | 3,786 (39.7)              |
| Step 5                                                                    | 26 (2.5)                             | 16 (0.6)                            | 13 (0.5)                            | 5 (0.1)                            | 60 (0.6)                  |
| Unclassified                                                              | 0 (0)                                | 1 (0)                               | 5 (0.2)                             | 8 (0.2)                            | 14 (0.1)                  |

(continued)

TABLE I. (Continued)

| Demographic characteristics/clinical features (2010)     | High-risk, high-adherent (N = 1,031) | High-risk, low-adherent (N = 2,472) | Low-risk, high-adherent (N = 2,505) | Low-risk, low-adherent (N = 3,538) | Entire cohort (N = 9,546) |
|----------------------------------------------------------|--------------------------------------|-------------------------------------|-------------------------------------|------------------------------------|---------------------------|
| Any ICS dispensing                                       |                                      |                                     |                                     |                                    |                           |
| None                                                     | 39 (3.8)                             | 560 (22.7)                          | 275 (11.0)                          | 527 (14.9)                         | 1,401 (14.7)              |
| Low dose                                                 | 152 (14.7)                           | 460 (18.6)                          | 358 (14.3)                          | 813 (23.0)                         | 1,783 (18.7)              |
| Medium dose                                              | 561 (54.4)                           | 1,113 (45.0)                        | 1,362 (54.4)                        | 1,741 (49.2)                       | 4,777 (50.0)              |
| High dose                                                | 279 (27.1)                           | 339 (13.7)                          | 510 (20.4)                          | 457 (12.9)                         | 1,585 (16.6)              |
| Any ICS/LABA dispensed                                   |                                      |                                     |                                     |                                    |                           |
| None                                                     | 470 (45.6)                           | 1,679 (67.9)                        | 1,201 (47.9)                        | 2,090 (59.1)                       | 5,440 (57.0)              |
| Low dose                                                 | 57 (5.5)                             | 110 (4.4)                           | 207 (8.3)                           | 318 (9.0)                          | 692 (7.2)                 |
| Medium dose                                              | 275 (26.7)                           | 409 (16.5)                          | 707 (28.2)                          | 789 (22.3)                         | 2,180 (22.8)              |
| High dose                                                | 229 (22.2)                           | 274 (11.1)                          | 390 (15.6)                          | 341 (9.6)                          | 1,234 (12.9)              |
| Leukotriene modifiers                                    | 352 (34.1)                           | 121 (4.9)                           | 1,079 (43.1)                        | 192 (5.4)                          | 1,744 (18.3)              |
| Theophylline                                             | 57 (5.5)                             | 8 (0.3)                             | 115 (4.6)                           | 11 (0.3)                           | 191 (2.0)                 |
| Omalizumab                                               | 7 (0.7)                              | 4 (0.2)                             | 1 (0.04)                            | 3 (0.1)                            | 15 (0.2)                  |
| Controller equivalent canisters dispensed, mean $\pm$ SD | 13.5 $\pm$ 4.9                       | 3.4 $\pm$ 2.6                       | 13.4 $\pm$ 4.7                      | 4.2 $\pm$ 2.5                      | 7.4 $\pm$ 5.8             |
| SABA canisters dispensed, mean $\pm$ SD                  | 10.7 $\pm$ 5.7                       | 10.4 $\pm$ 4.7                      | 2.1 $\pm$ 2.0                       | 3.1 $\pm$ 2.0                      | 5.5 $\pm$ 5.1             |
| $\geq 7$ SABA canisters dispensed                        | 882 (85.5)                           | 2,180 (88.2)                        | 0 (0)                               | 0 (0)                              | 3,062 (32.1)              |
| Asthma exacerbation rate/y (95% CI)                      | 0.82 (0.75-0.90)                     | 0.67 (0.63-0.72)                    | 0.15 (0.14-0.17)                    | 0.21 (0.19-0.22)                   | 0.38 (0.37-0.39)          |
| $\geq 1$ asthma exacerbation                             | 419 (40.6)                           | 896 (36.2)                          | 383 (15.3)                          | 730 (20.6)                         | 2,428 (25.4)              |
| $\geq 2$ asthma exacerbations                            | 256 (24.8)                           | 495 (20.0)                          | 0 (0)                               | 0 (0)                              | 751 (7.9)                 |
| $\geq 1$ asthma ED visit or hospitalization              | 97 (9.4)                             | 273 (11.0)                          | 41 (1.6)                            | 221 (6.2)                          | 632 (6.6)                 |

ICS, Inhaled corticosteroid; LABA, long-acting  $\beta_2$ -agonist; SABA, short-acting  $\beta_2$ -agonist.

Data as n (%) or as noted.

\* $P < .001$  for all across-group comparisons by chi-square test (categorical) and Wilcoxon rank sum test (continuous) analyses except  $P < .05$  for nasal polyps and  $P > .1$  for Medicare, Private Pay insurance, and eczema.

†Patients may have more than 1 insurance plan.

TABLE II. Comparison of asthma outcomes in 2011 among adult patients with persistent asthma based on asthma risk level and adherence to controller medication in 2010

| Asthma outcomes (2011)                             | Asthma risk level and adherence to controller medication (2010) |                                     |                                     |                                    | P value |
|----------------------------------------------------|-----------------------------------------------------------------|-------------------------------------|-------------------------------------|------------------------------------|---------|
|                                                    | High-risk, high-adherent (N = 1,031)                            | High-risk, low-adherent (N = 2,472) | Low-risk, high-adherent (N = 2,505) | Low-risk, low-adherent (N = 3,538) |         |
| Asthma exacerbation rate per patient-year (95% CI) | 0.51 (0.45-0.58)                                                | 0.47 (0.43-0.51)                    | 0.22 (0.20-0.25)                    | 0.23 (0.21-0.25)                   | <.001*  |
| $\geq 1$ asthma exacerbation, n (%)                | 314 (30.5)                                                      | 701 (28.4)                          | 427 (17.0)                          | 600 (17.0)                         | <.001†  |
| $\geq 2$ asthma exacerbations, n (%)               | 118 (11.4)                                                      | 261 (10.6)                          | 98 (3.9)                            | 154 (4.4)                          | <.001†  |
| $\geq 1$ asthma ED visit or hospitalization, n (%) | 56 (5.4)                                                        | 202 (8.2)                           | 60 (2.4)                            | 115 (3.3)                          | <.001†  |
| $\geq 7$ SABA canisters dispensed, n (%)           | 603 (58.5)                                                      | 1,457 (58.9)                        | 142 (5.7)                           | 305 (8.6)                          | <.001†  |

SABA, Short-acting  $\beta_2$ -agonist.

\*Chi-square test based on likelihood ratio statistics used to compare exacerbation rates among groups in the negative binomial model.

†Chi-square test based on quasi score statistics used to compare risks of various outcomes among groups in robust Poisson models.

the high-risk, high-adherent subgroup exhibited markedly higher rate and risk ratios for asthma exacerbations and risk ratios for 7 or more SABA canisters dispensed in 2011 ( $P < .001$ ) (Table III). However, compared with the high-risk, low-adherent subgroup, increased adherence in the high-risk, high-adherent subgroup was associated with reduced risk for asthma ED/hospitalizations (risk ratio, 0.75; 95% CI, 0.56-0.99;  $P = .045$ ), although no differences for other asthma outcomes were observed (Table III). Other covariates significantly

associated with many increased asthma exacerbation outcomes were female sex, ethnicity (Asians, Blacks, Hispanics vs Whites), obesity, higher Charlson comorbidity index, rhinitis, chronic sinusitis, pneumonia, and higher GINA step-care level (see Table E2 in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). Covariates significantly associated with excessive SABA dispensing were female sex, black versus white ethnicity, obesity, ever versus never smoked, state insurance programs, rhinitis, chronic sinusitis, and eczema (Table E2, in this article's

**TABLE III.** Adjusted rate ratio and risk ratio (95% CI)\* of asthma outcomes in 2011 comparing high-risk, high-adherent adult patients with persistent asthma to patients with other levels of risk and adherence in 2010

| Asthma outcomes (2011)                | Asthma risk level and adherence to asthma controller medication (2010) |                                           |                                            |
|---------------------------------------|------------------------------------------------------------------------|-------------------------------------------|--------------------------------------------|
|                                       | High-risk, high-adherent in 2010 (N = 1,031)                           |                                           |                                            |
|                                       | vs                                                                     |                                           |                                            |
|                                       | Low-risk, high-adherent (2010) (N = 2,505)                             | Low-risk, low-adherent (2010) (N = 3,538) | High-risk, low-adherent (2010) (N = 2,472) |
| Asthma exacerbation rate/y            | 2.02 (1.73-2.35) <sup>†</sup>                                          | 1.86 (1.61-2.15) <sup>†</sup>             | 0.92 (0.80-1.06)                           |
| ≥1 asthma exacerbation                | 1.64 (1.45-1.86) <sup>†</sup>                                          | 1.60 (1.43-1.80) <sup>†</sup>             | 0.95 (0.85-1.06)                           |
| ≥2 asthma exacerbations               | 2.57 (1.99-3.32) <sup>†</sup>                                          | 2.15 (1.71-2.70) <sup>†</sup>             | 0.87 (0.71-1.07)                           |
| ≥1 asthma ED visit or hospitalization | 1.82 (1.28-2.58) <sup>†</sup>                                          | 1.63 (1.20-2.21) <sup>‡</sup>             | 0.75 (0.56-0.99) <sup>§</sup>              |
| ≥7 SABA canisters dispensed           | 9.95 (8.41-11.78) <sup>†</sup>                                         | 6.85 (6.08-7.71) <sup>†</sup>             | 1.04 (0.98-1.11)                           |

SABA, Short-acting  $\beta_2$ -agonist.

\*Negative binomial and Poisson regression models with robust error variance were used to estimate the adjusted rate ratio and risk ratio, respectively, and their 95% CIs and to derive the *P* values. Adjusted for the following in 2010: age, sex, race/ethnicity, various types of health insurance, length of MCO enrollment, obesity, comorbidities, smoking status, asthma specialist care, and GINA step-care level (see Table E2 for details).

<sup>†</sup>*P* ≤ .001.<sup>‡</sup>*P* < .01.<sup>§</sup>*P* = .045.

Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). Allergist care was significantly associated with lower frequency of 2 or more asthma exacerbations and excessive SABA dispensing (Table E2, in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)).

To our knowledge, this is the first study to characterize and determine future asthma burden on the basis of previous levels of asthma risk and treatment adherence using electronic administrative pharmacy and health care utilization data in a large managed care organization. The study clearly showed that compared with low-risk patients in 2010, high-risk patients (≥2 asthma exacerbations or ≥7 SABA canisters dispensed) exhibited markedly greater asthma burden in a follow-up year. These findings in high-risk adult patients with asthma are consistent with the report from The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens study that noted that despite Expert Panel-3 step-care levels 4/5/6 and multiple long-term controller medications, adolescent and adult patients with severe or difficult-to-treat asthma manifested significant clinical burden and risk of future asthma exacerbations.<sup>9</sup> In multivariate analyses, high adherence to current therapy did not appear to improve most measured asthma outcomes compared with lower adherence in high-risk patients with asthma, although increased adherence appeared to help reduce more severe exacerbations (ED/hospitalizations) (Table III). The current findings are consistent with observations in a recent administrative study that found that compliance with the HEDIS adherence measure did not relate to improvement in asthma outcomes in a future year in patients with persistent asthma.<sup>10</sup>

This study has some limitations. The retrospective design with administrative data allowed us to capture only dispensings but not actual controller use or proper use including inhaler technique. Spirometry was unavailable for most patients with asthma in our administrative data, but the HEDIS definition of asthma, which does not include spirometry, is routinely used to identify patients with persistent asthma for administrative data studies and regulatory activities.<sup>11</sup>

The present study characterizes an important high-risk uncontrolled, high-adherent adult population with persistent asthma with a high level of future asthma burden despite the majority being dispensed at least GINA step-care level 4 controller

therapies. In addition, this population manifests a high frequency of asthma-relevant comorbidities that may contribute to poorer asthma control or complicate asthma diagnosis and treatment. These findings also suggest that it will take more than just dispensing high amounts of asthma controller medication to reduce asthma burden substantially in high-risk adults with persistent asthma. The higher disease burden despite adherence to existing asthma controller therapies suggests that to improve outcomes in this population, health care organizations and clinicians need to promote higher level step-care,<sup>12</sup> increased referral to allergist care, attention to relevant comorbidities, and judicious use of existing and novel new biologicals, when available.

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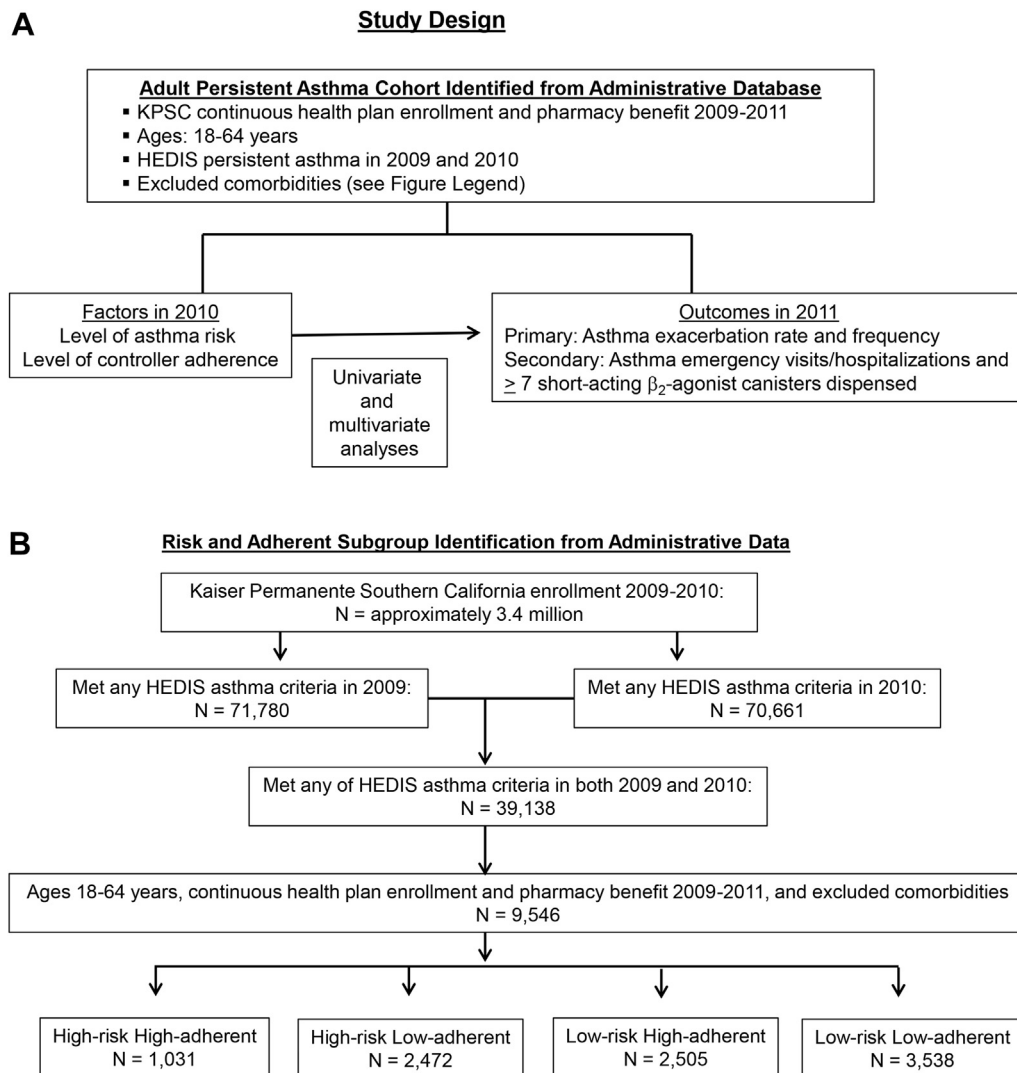


**FIGURE E1.** The study design, administrative logistics for patient identification, and number of patients identified with administrative databases. **A**, Summary of study design. Excluded patients had encounter diagnoses of chronic obstructive lung disease; emphysema; cystic fibrosis; chronic bronchitis; bronchiectasis; Churg Strauss syndrome; Wegener syndrome; sarcoidosis; pulmonary hypertension; cerebral palsy; transplantation of major organs (2004-2010); and other clinically relevant nonasthma pulmonary disorders, such as autoimmunity, immune deficiency, immunosuppression treatments (procedural codes), cancer, HIV, drug addiction, and major psychiatric disorders (2009-2010). **B**, An administrative algorithm for patient identification of the adult cohort with persistent asthma based on levels of risk and adherence defined as follows: (1) high-risk:  $\geq 2$  asthma exacerbations or  $\geq 7$  SABA canisters dispensed, (2) low-risk:  $< 2$  asthma exacerbations and  $< 7$  SABA canisters dispensed, (3) high-adherence:  $\geq 9$  controller canister equivalents dispensed, and (4) low-adherence:  $< 9$  controller canister equivalents dispensed. KPSC, Kaiser Permanente Southern California.

**TABLE E1.** Comparison of outcomes in 2011 among adult patients with persistent asthma based on asthma risk level in 2010

| Asthma outcomes (2011)              | High-risk (N = 3,503) | Low-risk (N = 6,043) | Unadjusted rate or risk ratio (95% CI) | P value |
|-------------------------------------|-----------------------|----------------------|----------------------------------------|---------|
| Asthma exacerbation rate/y (95% CI) | 0.48 (0.45-0.52)      | 0.23 (0.21-0.24)     | 2.12 (1.93-2.32)                       | <.001*  |
| ≥1 asthma exacerbation, n (%)       | 1,015 (29.0)          | 1,027 (17.0)         | 1.70 (1.58-1.84)                       | <.001†  |
| ≥2 asthma exacerbations, n (%)      | 379 (10.8)            | 252 (4.2)            | 2.59 (2.22-3.03)                       | <.001†  |
| ≥1 asthma ED/hospitalization, n (%) | 258 (7.4)             | 175 (2.9)            | 2.54 (2.11-3.07)                       | <.001†  |
| ≥7 SABA canisters dispensed, n (%)  | 2,060 (58.8)          | 447 (7.4)            | 7.95 (7.24-8.73)                       | <.001†  |

SABA, Short-acting  $\beta_2$ -agonist.

\*Chi-square test based on likelihood ratio statistics used to compare exacerbation rates among groups in the negative Binomial model.

†Chi-square test based on quasi score statistics used to compare risks of various outcomes among groups in robust Poisson models.

**TABLE E2.** Adjusted rate ratio and risk ratio (RR) (95% CI)\* of asthma outcomes for each covariate (2010) being controlled for in the regression models

| Covariates (2010)                  | Asthma outcomes (2011)    |                  |                  |                       |                             |
|------------------------------------|---------------------------|------------------|------------------|-----------------------|-----------------------------|
|                                    | Exacerbation rate (no./y) | ≥1 exacerbation  | ≥2 exacerbations | ≥1 ED/hospitalization | ≥7 SABA canisters dispensed |
| Age (1-y increment)                | Not selected              | Not selected     | Not selected     | 0.98 (0.97-0.98)      | Not selected                |
| Female vs male                     | 1.31 (1.19-1.45)          | 1.24 (1.14-1.34) | 1.31 (1.11-1.55) | Not selected          | 0.87 (0.83-0.92)            |
| Asian vs white                     | 1.29 (1.08-1.53)          | 1.25 (1.08-1.44) | 1.32 (0.99-1.75) | 1.97 (1.39-2.80)      | 1.07 (0.96-1.20)            |
| Black vs white                     | 1.45 (1.27-1.65)          | 1.34 (1.20-1.50) | 1.49 (1.21-1.84) | 3.08 (2.42-3.93)      | 1.13 (1.05-1.22)            |
| Hispanic vs white                  | 1.31 (1.17-1.46)          | 1.27 (1.16-1.39) | 1.30 (1.08-1.56) | 1.69 (1.32-2.16)      | 1.0 (0.93-1.08)             |
| State insurance† (Y/N)             | Not selected              | 0.84 (0.70-1.0)  | Not selected     | Not selected          | 1.24 (1.11-1.37)            |
| Private insurance (Y/N)            | 0.64 (0.50-0.80)          | 0.70 (0.57-0.86) | 0.51 (0.32-0.83) | Not selected          | Not selected                |
| Membership (1-y increment)         | 0.99 (0.99-1.0)           | 1.0 (0.99-1.0)   | Not selected     | Not selected          | Not selected                |
| Smoking (ever/never)               | Not selected              | Not selected     | Not selected     | 1.29 (1.06-1.57)      | 1.06 (1.0-1.13)             |
| Obesity (Y/N)                      | 1.18 (1.07-1.29)          | 1.14 (1.06-1.24) | 1.16 (0.99-1.36) | Not selected          | 1.07 (1.01-1.14)            |
| Charlson comorbidity index ≥3 vs 0 | 2.08 (1.62-2.66)          | 1.86 (1.50-2.31) | 3.19 (2.07-4.94) | 2.07 (1.24-3.45)      | Not selected                |
| Rhinitis (Y/N)                     | 1.18 (1.07-1.30)          | 1.14 (1.05-1.23) | 1.37 (1.15-1.64) | Not selected          | 0.85 (0.78-0.92)            |
| Chronic sinusitis (Y/N)            | 1.32 (1.17-1.49)          | 1.24 (1.13-1.36) | 1.36 (1.13-1.65) | Not selected          | 0.84 (0.76-0.93)            |
| Nasal polyps (Y/N)                 | 1.55 (1.16-2.08)          | Not selected     | 1.55 (1.05-2.29) | Not selected          | Not selected                |
| Pneumonia (Y/N)                    | 1.70 (1.39-2.09)          | 1.61 (1.41-1.84) | 1.64 (1.25-2.14) | 1.90 (1.37-2.64)      | Not selected                |
| Gastroesophageal reflux (Y/N)      | Not selected              | Not selected     | Not selected     | Not selected          | 0.89 (0.81-0.98)            |
| Eczema (Y/N)                       | Not selected              | Not selected     | Not selected     | Not selected          | 1.36 (1.14-1.62)            |
| GINA care level: High vs low       | 1.49 (1.31-1.69)          | 1.35 (1.21-1.50) | 1.72 (1.38-2.13) | Not selected          | Not selected                |
| Allergist care (Y/N)               | Not selected              | Not selected     | 0.82 (0.67-1.0)  | 1.23 (0.98-1.54)      | 0.86 (0.78-0.96)            |

N, No; SABA, short-acting  $\beta_2$ -agonist; Y, yes.

\*Negative binomial regression was used to estimate the adjusted rate ratio, and Poisson regression with robust error variance was applied to estimate the adjusted RR. A manual selection process was used, and only those variables that were presented in the above table were retained in the final models.

†MediCAL or other state programs.

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